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(54) Washing composition capable of preventing and ameliorating skin irritation.

(57) A washing composition containing one or more compounds having a protease inhibitory activity and dermatologically acceptable components.

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BACKGROUND OF THE INVENTION

1. Field of the Invention

5 The present invention relates to a novel washing agent. More specifically, it relates to a detergent composition for domestic or business use or a skin cleanser composition comprising one compound or two or more compounds selected from compounds having a protease inhibitory activity, which prevents and ameliorates skin irritation, and at the same time, is harmless to the human body and has a strong washing power.

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2. Description of the Related Art

Washing compositions such as cleansers and detergents have been generally employed for removing contaminants or soils attached to the surface or internally of materials and the human body, and may be 15 broadly classified into 1) those used for the human body, 2) those used for clothing and fiber products, 3) and those for washing soft and rigid surfaces.

Among these cleansers, the cleanser for the human body (i.e., skin) is intended to remove the fat and sweat secreted from the skin surface, and other corneum cells detached as a result of metabolism (i.e., dirt), outside contamination attached thereto, and cosmetics.

20 The surfactant contained in a detergent is a chemical exhibiting a washing power and foaming power which are inherent properties of the detergent, but these are known to have an adverse influence on human skin. A detergent which comes directly into contact with human skin must produce only a weak irritation of the skin or eyes.

For skin cleansers, surfactants with a low irritation effect have been developed to obtain useful products, 25 but there remains a need to improve the washing power and foaming power thereof.

For the washing of the human body, surfactants with a low irritation effect have been developed to obtain useful products, but there remains a need to improve the washing power and foaming power, and a product which fully satisfies users has not yet been developed. Further, even though the composition has a low irritation effect, it would be more useful if a chemical which treats and ameliorates skin irritation were 30 formulated therein.

On the other hand, currently, for washing objects other than the human body, the surfactants primarily used have a strong washing power but also cause an irritation of the skin or eyes. Although efforts to improve safety have been made by working with the use of protective tools such as gloves, or by way of after-care after completion of the work, the sensitivity of the fingertips may be lost depending the work, and 35 thus the wearing of gloves may be unsuitable in some cases; sometimes skin irritation is reported to be generated by the gloves per se. Also, although the practice of after-care after the completion of work is important, it is considered more useful if the chemical acts during the work.

Many proteases are known to exist, which maintain the structure and constancy of the skin functions, and the important role thereof thus recently attracted more attention. A protease or proteolytic enzyme is 40 the comprehensive name for enzymes which catalyze a peptide bond by hydrolysis, and such proteases are classified into peptidases and proteinases. The former are enzymes which cleave the peptide bond from the outside of the amino group terminal end or the carboxyl group terminal end of a protein or a peptide chain, and the latter proteinase are enzymes which cleave the specific bond internally of a peptide chain. Such proteinases are known as "protease" in a broad sense, and further, are broadly classified, according 45 to the properties of their active sites, into 1) serine type, 2) thiol (cysteine) type, 3) carboxyl type and 4) metal proteinase, and specific inhibitors exist for the respective enzymes.

SUMMARY OF THE INVENTION

50 The objects of the present invention are to obviate the above-mentioned problems of the prior art and to provide a washing composition containing one or more compounds having a protease inhibitory activity, which prevents and ameliorates skin irritation, and is harmless to the human body and has a strong washing power.

Other objects and advantages of the present invention will be apparent from the following description.

55 In accordance with the present invention, there is provided a washing composition comprising at least one compound having a protease inhibitory activity and dermatologically acceptable components for a conventional washing composition.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present inventors, in view of the state of the art as described above, have made an intensive study of the relationship between various chemicals and skin irritation treatment and amelioration, for treating and ameliorating skin irritation by formulating an effective chemical in the detergent itself, which has not been practiced in the prior art, and consequently, found that a washing composition formulated with a protease inhibitor provides an excellent amelioration of skin irritation, and accomplished the present invention based on thus finding.

The constitution of the present invention is now described as follows.

More specifically, the first aspect of the present invention concerns a detergent for domestic or business use, comprising one or two or more compounds selected from compounds having a protease inhibitory activity.

The detergent composition for domestic or business use of the present invention includes washing detergents for domestic use, washing detergents for business use (laundry detergents, dry cleaning detergents), washing aids (softeners, bleaching agents, glue agents, water repellents), stain remover, carpet shampoo, rust remover, detergents for kitchen (for vegetables, fruits, dish, cooking tools, etc.), oven cleaner, floor polish, floor wax, floor cleaner, floor wax remover, stain remover of floor, window glass detergent, blind cleaner, toilet stool detergent, porcelain detergent, marble detergent, stone wall detergent, wall paper detergent, wall paper and label peeling agent, paint face detergent, paint peeling agent, plastic cleaner, metal face detergent, furniture polisher, slippery agent of door, paper screen, automobile body detergent, car polish, automobile part detergent (type cleaner, inner engine carbon remover, radiator cleaner, mechanical part detergent electrical insulator detergent, brake lining cleaner, etc.), aircraft detergent, metal detergent (iron, copper and general metal detergent, stainless steel and chromium face detergent, aluminum detergent copper and copper alloy detergent silver detergent, etc.), detergents for press for printing, rolls ink bottle, etc., detergents for dairy industries, tank detergents, discharge pipe, sewage reservoir detergent, leather product detergent, shoe cleaner, shoe polish, spectacle lens cleaner, artificial tooth cleaner, refrigerator detergent, deodorant, road detergent, etc.

The second aspect of the present invention concerns a skin cleanser composition comprising one or two or more compounds selected from compounds having a protease inhibitory activity.

The skin cleanser composition of the present invention is intended to remove various contaminants attached to the human body, and from animals such as pets and domestic stock.

Specifically, the following compositions may be included in the second aspect of the present invention, but it is not limited thereto.

The compositions include soap, hand cleansers, body shampoos, body lotions, pre-shaving lotions, shaving foams, cleansing creams, cleansing lotions, and pet shampoos.

A protease or proteolytic enzyme is the comprehensive name for enzymes which catalyze a peptide bond by hydrolysis, and such proteases are classified into peptidases and proteinases. The former are enzymes which cleave the peptide bond from the outside of the amino group terminal end or the carboxyl group terminal end of a protein or a peptide chain, and the latter proteinase are enzymes which cleave the specific bond internally of a peptide chain. Such proteinases are known as "protease", in a broad sense, and further, are broadly classified, according to the properties of their active sites, into 1) serine type, 2) thiol (cysteine) type, 3) carboxyl type and 4) metal proteinase, and specific inhibitors exist for the respective enzymes.

The protease inhibitor or the compound having a protease inhibitory activity usable in the present invention includes all the chemical substances capable of inhibiting, reversibly or irreversibly, the hydrolysis activity of the above protease or proteolytic enzyme.

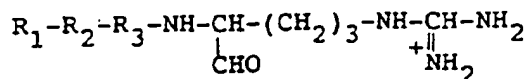
Specifically, the following substances are included.

(1) Compounds derived from animals or vegetables:

preferably a bovine pancrea basic trypsin inhibitor, aprotinin, soybean trypsin inhibitor, rimabeane protease inhibitor, and corn protease inhibitor.

(2) Compounds derived from microorganisms:

preferably antipine, plasminostreptin, and further, compounds comprehensively known as leupeptin and represented by the following formula:



$R_1 = \text{CH}_3\text{CO}, \text{CH}_3\text{CH}_2\text{CO}$

$R_2 = \text{L-Leu}, \text{L-Ile}, \text{L-Val}$

$R_3 = \text{L-Leu}, \text{L-Ile}, \text{L-Val}$

(Leu: leucine, Ile: isoleucine, Val: valine)

5 (3) Benzamidine and derivatives thereof:

preferably benzamidine, p-aminobenzamidine, m-aminobenzamidine, phenylguanodine, (2R,4R)-4-methyl-1-[N²-(3-methyl-1,2,3,4-tetrahydro-8-quinolinesulfonyl)-L-arginyl]-2-piperidinecarboxylic acid monohydrate, and dancylarginine N-(3-ethyl-1,5-pentanediy)amide.

(4) Acetamide and derivatives thereof:

10 preferably acetamide and 2-phenylacetamide, cyclohexylacetamide.

(5) Guanidine and derivatives thereof:

preferably phenylguanidine and cyclohexylguanidine.

(6) ω -amino acids:

15 Preferably tranexamic acid, p-aminomethylbenzoic acid, 4-aminomethylbicyclo(2,2,2)octane-1-carboxylic acid, 5-[trans-4(aminomethyl)cyclohexyl]-tetrazole, 3-[trans-4(aminomethyl)cyclohexyl]-2-oxopropionate, trans-4-(aminomethyl)cyclohexyl glyoxal monohydrate, and trans-4-(aminomethyl)-cyclohexane hydroxamic acid, or substances represented by the following formula wherein the carbon chain has $n = 1 - 8$:

20 $\text{NH}_2(\text{CH}_2)_n\text{COOH}.$

The present invention is not limited to the above, but among these ω -amino acids, particularly good effects can be recognized in ϵ -aminocaproic acid and tranexamic acid, and in p-aminomethylbenzoic acid.

25

(7) Fluorophosphoric acid and derivatives thereof:

preferably diisopropylfluorophosphoric acid.

(8) Fluorosulfonic acid and derivatives thereof:

preferably phenylmethanesulfonyl fluoride, and [(p-amidinophenyl)methanesulfonyl fluoride.

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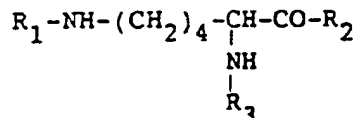
(9) Guanidinobenzoic acid and derivatives thereof:

Preferably p-nitrophenyl-p'-guanidinobenzoic acid, 3',6'-bis(4-guanidinobenzoyloxy)-5-(N'-4-carboxyphenyl)thioureidospiro[isobenzofuran-1(3H) 9'-(9H)xanthen]-3-one.

(10) Lysine and derivatives thereof:

preferably, compounds represented by the following formula:

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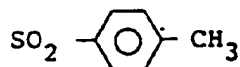
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$R_1 = \text{H}, \text{Phe-Ala}, \text{Ala-Phe}$

$R_2 = \text{OH}, \text{CH}_2\text{Cl}$

$R_3 = \text{H}.$

45



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(Phe: phenylalanine, Ala: alanine)

The present invention is not limited to the above, but among these lysine and derivatives thereof, a particular good effect is recognized in $R_2 = \text{CH}_2\text{Cl}$.

(11) Arginine and derivatives thereof:

55

preferably the compounds represented by the following formula:

CS(=O)(=O)c1ccccc1

15

The present invention is not limited to the above, but among these arginind and derivatives thereof, a particularly good effect is recognized in $R_2 = CH_2Cl$.

In the present invention, the compounds having a protease inhibitory activity as mentioned above can be used alone or in any combination thereof.

The "skin irritation treatment and amelioration effect" as mentioned in the present invention means the activity as shown below.

In the washing composition of the present invention, in addition to the compounds having a protease inhibitory activity, there can be formulated, if necessary, pharmaceutically or dermatologically acceptable surfactants (anionic, cationic, nonionic, amphoteric, semipolar) aids (builder), abrasives, fluorescent brightness, bleaching agents, colorants, preservatives, sequestering agents, antistatic agents, precipitation preventives, antioxidants, perfumes, oils, humectants, and chemicals such as antipilogic agents, sterilizers, and vitamins within the range which does not impair the effect of the present invention.

i) fatty acid soap type anionic surfactants represented by the formula:

(wherein R represent an alkyl group or alkenyl group having 8 to 18 carbon atoms, M represents one or two or more of alkali metals, organic amines, and basic amino acids);

ii) ether carboxylic acid salt type anionic surfactants represented by the formula:

45

$$R(OCH_2CH_2)_nOCH_2COOM$$

(wherein R represents an alkyl group or alkylallyl group having 8 to 22 carbon atoms, n is an integer of 1 to 16, and M represents one or two or more of alkali metals, organic amines, and basic amino acids);

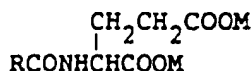
50 iii) N-acylsarcosine salt type anionic surfactants represented by the formula:



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iv) anionic surfactants having a
-COO⁻ group

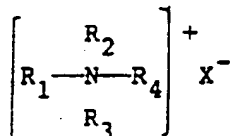
in the formula represented by condensed products of higher fatty acids and amino acids such as N-acylglutamic acid salts represented by the formula:



(wherein R represents an alkyl group or alkenyl group having 8 to 18 carbon atoms, and M represents one or two or more of alkali metals, organic amines, and basic amino acids).

More specifically, anionic surfactants can include base materials for soap; fatty acid soaps such as sodium laurate, sodium palmitate or the like; higher alkyl sulfate salts such as sodium lauryl sulfate, potassium lauryl sulfate or the like; alkyl ether sulfate salts such as triethanolamine polyoxyethylene (hereinafter abbreviated as POE) lauryl sulfate, sodium POE lauryl sulfate or the like; N-acylsarcosine such as sodium lauroylsarcosinate or the like; higher fatty acid amide sulfonic acid salts such as sodium N-myristoyl-N-methyltaurine, sodium coconut oil fatty acid methyltauride, sodium lauryl methyltauride or the like; phosphate salts such as sodium POE oleyl ether phosphate, and POE stearyl ether phosphoric acid or the like; alkylhydroxycarboxylic acid salts such as sodium laurylhydroxy ether carboxylate or the like; sulfosuccinic acid salts such as sodium di-2-ethylhexylsulfosuccinate, sodium monolauroyl mon-oethanolamide polyoxyethylene sulfosuccinate, and sodium lauryl polypropylene glycol sulfosuccinate or the like; alkylbenzene sulfonic acid salts such as sodium linear dodecylbenzene sulfonate, triethanolamine linear dodecylbenzene sulfonate, and linear dodecylbenzene sulfonic acid or the like; N-acylglutamate salts such as monosodium N-lauroylglutamate, disodium N-stearoylglutamate, and monosodium N-myristoyl-L-glutamate or the like; higher fatty acid ester sulfuric acid salts such as sodium hardened coconut oil fatty acid glycerine sulfate or the like; sulfated oil such as Turkey red oil; POE alkyl ether carboxylic acids, POE alkylallyl ether carboxylic acid salts, α -olefinsulfonic acid salts, higher fatty acid ester sulfonic acid salts, secondary alcohol sulfonate salts, higher fatty acid alkylolamide sulfate salts, sodium lauroyl mon-oethanolamide succinate, di-triethanolamine N-palmitoylaspartate, and sodium caseinate, and so on.

The cationic surfactants include monoalkyl type quaternary ammoniums salts represented by the formula:



(wherein R₁ represents an alkyl group or alkenyl group having 12 to 22 carbon atoms, R₂, R₃ and R₄ represent methyl or ethyl group, X represents a halogen atom or a methyl sulfate residue), and further, aliphatic amine salts, aromatic quaternary ammonium salts, pyridinium salts, and imidazolinium salts.

The nonionic surfactants can include glycerine fatty acid esters, sorbitane fatty acid esters sorbitol fatty acid esters, sucrose fatty acid esters, polyoxyethylene (hereinafter called POE) sorbitane fatty acid ester, polyoxyethylene glycol fatty acid esters, POE alkyl ethers, POE alkylphenyl ethers, POE hardened castor oil derivatives, mannitol hydroxyfatty acid ethers, and alkylglycoside fatty ethers.

The amphoteric surfactants can include carboxybetaines such as N,N-dimethylauryl-N-carboxymethylammonium betaine, N,N-dimethyl-N-oleyl-N-carboxymethylammonium betaine, and lauryldimethylaminoacetic acid or the like; imidazoline derivatives such as 2-lauryl-N-carboxyethyl-N-hydroxyethylimidazolinium betaine, 2-lauryl-N-carboxymethyl-N hydroxyethylimidazolinium betaine, 2-undecyl-N,N,N-(hydroxyethylcarboxymethyl)-2-imidazoline sodium, and 2-cocoyl-2-imidazolinium hydroxide-1-carboxyethoxy-2-sodium or the like; aminocarboxylic acid salts such as sodium N-coconutalkyl- β -aminopropionate and sodium N-coconutalkyl- β -iminodipropionate or the like, and sulfobetaine and aminobetaine.

The semi-polar surfactants can include lauryldimethylamine oxide, stearyldimethylamine oxide, and bis-(2-hydroxyethyl)lauryl-amine oxide.

As the propellant, all propellants which can be used in aerosol products in general are applicable. Specifically, there include fluorinated hydrocarbons such as Freon 11 (registered trade mark) Freon 12

(registered trade mark), Freon 21 (registered trade mark), Freon 113 (registered trade mark), and Freon 114 (registered trade mark), liquefied petroleum gas (L. P. G.) which is a mixture of propane, isobutane, n-butane, and a compressed gas such as carbon dioxide gas and nitrogen gas. These gases can be used either alone or as a mixture of two or more kinds thereof, and the amount formulated is generally 2 to 20% by weight. With an amount of 2% or less, the internal pressure may be lower, and thus the stock liquid may not be properly emitted upon use, and on the other hand, further improved results cannot be obtained if 20% or more of the gas is employed; conversely, the internal pressure may become too high.

Any conventionally used water-insoluble oil may be employed, for example, higher alcohols such as cetyl alcohol, stearyl alcohol, and cholesterol or the like; higher fatty acids having $C_8 - C_{22}$ carbon atoms such as lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, and isostearic acid or the like; waxes such as solid paraffin, microcrystalline wax, polyethylene wax, canderilla wax, beeswax, hardened castor oil, carunaba was, and barico wax or the like; animals and vegetable oils such as tallow, lard, sheep oil, squalane, coconut oil, palm oil, palmkernel oil, soybean oil, olive oil, cottonseed oil, jojoba oil, castor oil, and lanolin; mineral oils such as fluid paraffin and petrolatum; and synthetic oils such as trimethylpropane triisostearate, isopropyl myristate, glycerol tri-2-ethylhexanate, pentaerythritol tetra-2-ethylhexanate, silicone oil, and polyoxyethylene polyoxypropylene pentaerythritol ether.

Any conventionally used polyhydric alcohol may be employed, for example, propylene glycol, dipropylene glycol, glycerine, 1,3-butylene glycol, polyethylene glycol, polyoxyethylene methylglycoside ether, polyoxyalkylene diglyceryl ether, polyoxyalkylene polyglyceryl ether, polyoxyalkylene decaglyceryl ether, polyoxyalkylene pentaerythritol ether, sorbitol, maltitol, lactose, and D-mannitol.

Further, there can be included sterilizers such as cetylpyridinium chloride, benzetonium chloride, decalinium chloride, benzalkonium chloride, chlorohexydine gluconate, carbanilide, phenol, and halogenated salicylanilide, alkalis such as caustic potash and ammonia, lower alcohol such as ethanol, and humectants such as mucopolysaccharides and pyrrolidone carboxylic acid salts, etc. Other humectants are propylene glycol, dipropylene glycol, glycerine, 1,3-butylene glycol, polyethylene glycol, polyoxyethylene methylglycoside ether, polyoxyalkylene diglyceryl ether, polyoxyalkylene polyglyceryl ether, polyoxyalkylene decaglyceryl ether, polyoxyalkylene pentaerythritol ether, sorbitol, maltitol, lactose, D-mannitol, mucopolysaccharide, and pyrrolidone carboxylic acid salts.

The abrasives usable in the detergent composition for domestic or business use include silicates such as sodium metasilicate or the like, salts such as sodium sulfate and sodium carbonate, silica, borax, talc, diatomaceous earth, bentonite, colloidal clay, fluorite, quartz, and sand.

The washing composition according to the present invention may be in any desired form, as long as it is in the form suitable for accomplishing the object of providing a detergent, as exemplified by a liquid (lotion, milky lotion), cream, solid, fine granules, and powder.

The washing composition of the present invention can be used while washing, and prevents and ameliorates skin irritation, and at the same time, is harmless to the human body and has a strong washing power.

EXAMPLES

The present invention will now be further illustrated by, but is by no means limited to, the following Examples and Actual Use Examples.

Prior to the Examples, the test methods and evaluation methods practiced for clarifying the prevention of skin irritation and amelioration of skin irritation effects of the compound having a protease inhibitory activity according to the present invention are explained.

Actual Use Test I-1

Sixty housewives 40 to 60 years old and susceptible to "skin irritation" when continuously using conventional synthetic detergents in the kitchen were selected as the subjects to be tested and divided into 6 groups each having 10 members. For the subjects to be tested of 5 groups, the respective Examples shown in Table I-1 were used, and for the subjects to be tested of the remaining one group, Comparative Example I-1 was used. Continuous use tests were conducted for 4 weeks, and thereafter, the state of the skin of the back of the hands was observed by the replica method, and evaluated according to the judgement standards shown in Table I-2. Each recipe was prepared according to conventional methods, to obtain a synthetic detergent for kitchen.

Table I-1

	Example					Comparative Example
	I-1	I-2	I-3	I-4	I-5	I-1
Sodium POE (3 mole) alkyl ether sulfate	15.0	15.0	15.0	15.0	15.0	15.0
POE (15 mole) alkyl ether	5.0	5.0	5.0	5.0	5.0	5.0
Coconut fatty acid ethanol amide	6.0	6.0	6.0	6.0	6.0	6.0
Ethanol	1.0	1.0	1.0	1.0	1.0	1.0
Perfume	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Dye	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water	balance	balance	balance	balance	balance	balance
Tranexamic acid	1.0	-	-	-	-	-
Leupeptin	-	0.5	-	-	-	-
Tosylarginine	-	-	3.0	-	-	-
Tosylllysyl chlormethyl ketone	-	-	-	0.05	-	-
Soybean trypsin inhibitor	-	-	-	-	0.1	-

Table I-2

Score	Evaluation	Remarks
1	Disappearance of skin groove, skin rise Peeling of wide range of corneum	Irritated skin
2	Obscure skin groove, skin rise Partial peeling of corneum	↑ ↓
3	Skin groove, skin rise recognized, but flat	
4	Clear skin groove, skin rise	
5	Skin rise, skin groove clear and regular	Beautiful skin

Table I-3

Replica score	Example					Comparative Example
	I-1	I-2	I-3	I-4	I-5	I-1
1	0	0	0	0	0	2
2	0	0	0	0	0	2
3	0	0	1	2	1	5
4	2	1	1	1	4	1
5	8	9	8	7	5	0

The numerals in the Table indicate the number of the persons tested who exhibited the respective evaluation scores.

As shown by the results in Table I-3, the detergent compositions of the present invention (Examples I-1 - I-5) exhibited a superior effective to that of the detergent composition of the Control (Comparative Example I-1).

Example I-6 Liquid detergent for clothing

	(1) Na POE (3 mole) lauryl ether sulfate	15.0
	(2) POE (15 mole) alkyl ether	20.0
5	(3) Distearyl dimethylammonium chloride	2.0
	(4) Aprotinin	0.5
	(5) Bleaching agent	q.s.
	(6) Purified water	balance

10 Example I-7 Powder detergent for clothing

	(1) LAS-Na	15.0
	(2) Na_2SO_4	30.0
	(3) 2-Phenylacetamide	2.0
15	(4) CMC (66%)	1.5
	(5) Sodium metasilicate (anhydrous)	20.0
	(6) Fluorescent brightener	0.2
20	(7) Na_2CO_3	balance

Example I-8 Solid soap

	(1) Tallow	20.0
	(2) Coconut oil	12.0
25	(3) Castor oil	5.0
	(4) Olive oil	3.0
	(5) Caustic potash	6.0
	(6) Ethanol	20.0
30	(7) Glycerine	5.0
	(8) Sucrose	10.0
	(9) Cyclohexylguanidine	3.0
	(10) EDTA	0.1
35	(11) Perfume	q.s.
	(12) Dye	q.s.
	(13) Purified water	balance

40 Example I-9 Liquid soap

	(1) Lauric acid	3.0
	(2) Myristic acid	7.0
	(3) Palmitic acid	3.0
45	(4) Oleic acid	2.5
	(5) Lauroyl diethanolamide	6.0
	(6) Propylene glycol	11.0
	(7) Glycerine	4.0
50	(8) Sucrose	5.0

(9)	Caustic potash	3.0
(10)	EDTA	0.1
(11)	p-Aminobenzimidine	1.0
(12)	Perfume	q.s.
(13)	Purified water	balance

The respective compounds used in the following Examples were the compounds represented by the formula shown below, in which R_1 , R_2 , R_3 are respectively those shown in Table I-4.

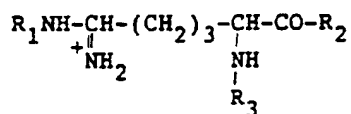
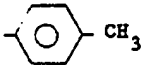
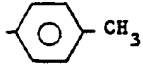


Table I-4

	R_1	R_2	R_3
Compound I-1	D-Phe-Pro	CH_2Cl	SO_2 - 
Compound I-2	Glu-Gly	CH_2Cl	SO_2 - 

(Phe: phenylalanine, Pro: proline, Glu: glutamic acid, Gly: glycine)

Example I-10 Detergent for kitchen

(1)	Na α -Oleylsulfonate	20.0
(2)	POE (15 mole) alkyl ether	8.0
(3)	Laurylamide propylbetaine	5.0
(4)	Ethanol	1.5
(5)	Compound I-1	3.5
(6)	Dye	q.s.
(7)	Perfume	q.s.
(8)	Purified water	balance

Example I-11 Detergent for kitchen

(1)	Monosodium N-lauroylglutamate	25.0
(2)	POE (15 mole) alkyl ether	5.0

	(3)	Lauryldimethylamine oxide	8.0
	(4)	Ethanol	1.0
5	(5)	Compound I-2	7.0
	(6)	Dye	q.s.
	(7)	Perfume	q.s.
10	(8)	Purified water	balance

All of the detergent compositions of Examples I-6 - I-11 were found to provide a superior skin irritation and skin irritation amelioration effect, to be harmless to the human body, and to have a strong washing power.

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Actual Use Test II-1

Sixty men 30 to 50 years old and susceptible to "razor irritation" were selected as the subjects to be tested and divided into 6 groups each having 10 members. For the subjects to be tested of 5 groups, the respective Examples shown in Table II-1 were used, and for the subjects to be tested of the remaining one group, Comparative Example II-1 was used. Continuous use tests were conducted for 4 weeks, and thereafter, the state of the skin back of the hand was observed and evaluated according to the standards given in Table II-2. Each recipe was prepared according to conventional methods, to obtain an aerosol shaving foam.

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Table II-1

	Example					Comparative Example
	II-1	II-2	II-3	II-4	II-5	II-1
C ₁₈ alkyltrimethylammonium chloride	4.2	4.2	4.2	4.2	4.2	4.2
Potassium myristoylglutamate	3.5	3.5	3.5	3.5	3.5	3.5
Lauryldimethylaminoacetic acid betaine	8.0	8.0	8.0	8.0	8.0	8.0
Glycerine	3.0	3.0	3.0	3.0	3.0	3.0
Perfume	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Dye	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water	balance	balance	balance	balance	balance	balance
Propellant (L.P.G.)	6.0	6.0	6.0	6.0	6.0	6.0
Leupeptin	0.3	-	-	-	-	-
Tranexamic acid	-	1.2	-	-	-	-
Tosyllysyl chlormethyl ketone	-	-	0.07	-	-	-
Tosylarginine	-	-	-	5.5	-	-
Soybean trypsin inhibitor	-	-	-	-	0.1	-

(The numerals in the Table show % by weight.)

Table II-2 Amelioration effect on razor irritation

5	Evaluation	Judgement standards	
	Remarkably effective	Razor irritation disappeared	
10	Effective	•	greatly ameliorated
	Slightly effective	•	slightly ameliorated
	Ineffective	•	not changed
15	Worsened	•	worsened

Table II-3

20	Judgement results by visual observation	Example					Comparative Example
25		II-1	II-2	II-3	II-4	II-5	
	Remarkably effective	8	9	6	8	6	0
30	Effective	2	1	3	1	2	1
	Slightly effective	0	0	1	1	1	2
	Ineffective	0	0	0	0	1	7
35	Worsened	0	0	0	0	0	0

40 The numerals in the Table show the number of the persons indicating the respective judgment results.
As shown by the results in Table II-3, the skin cleanser compositions of the present invention (Examples II-1 - II-5) exhibited a superior effective to that of the skin cleanser composition of the Control (Comparative Example II-1).

45 Actual Use Test II-2

Thirty women 25 to 40 years old and susceptible to skin irritation were selected as the subjects to be tested and divided into three groups each having 10 members. For the subjects to be tested of two groups, the respective Examples shown in Table II-4 were used, and for the remaining one group, the Comparative
50 Example II-2 was used, and face washing was practiced. The tests were practiced by continuous use for 4 weeks, and after completion of the test, the skin state of the cheek portion of the face was judged by the replica method. The judgment was conducted according to the standards shown in Table II-5, and the results were represented as the average of the panel of 10 members. The manner in which contaminants such as cosmetics, etc., were removed was judged by a self-evaluation by the panel members, following
55 the standards shown in Table II-6. Each recipe was prepared according to conventional methods, to obtain a cleansing foam.

Table II-4

5		Example		Comparative
		II-6	II-7	Example
10	Lauric acid	8.0	8.0	8.0
	Myristic acid	12.0	12.0	12.0
15	Palmitic acid	4.0	4.0	4.0
	Stearic acid	4.0	4.0	4.0
20	Glycerine monostearate	1.5	1.5	1.5
	POE glycerylmonostearate (60E.O.)	2.0	2.0	2.0
25	Glycerine	2.5	2.5	2.5
	Polyoxyethylene glycol (M.W. 500)	8.0	8.0	8.0
30	Sorbitol solution	5.0	5.0	5.0
	Caustic potash	5.5	5.5	5.5
35	Purified water	balance	balance	balance
	p-Aminobenzamidine	0.5	-	-
40	Tosyllysine	-	2.0	-

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Table II-5

Score	Evaluation	Remarks
5	1 Disappearance of skin groove, skin rise Peeling of wide range of corneum	Irritated skin
10	2 Obscure skin groove, skin rise Partial peeling of corneum	↑ ↓
	3 Skin groove, skin rise recognized, but flat	
15	4 Clear skin groove, skin rise	
	5 Skin rise, skin groove clear and regular	Beautiful skin

Table II-6

Evaluation	Contents
⊙	80% or more of the panel satisfied with good removal of contaminants.
o	60% " "
Δ	40% " "
x	Less than 40% " "

Table II-7

	Example		Comparative Example
	II-6	II-7	II-2
Replica score	4.8	4.7	2.9
Extent of contaminate removal	⊙	⊙	⊙

As shown by the results given in Table II-7, the skin cleanser compositions (Examples II-6 and II-7) exhibited a superior effective to that of the skin cleanser composition of the Control (Comparative Example II-2).

Example II-8 Solid soap

		% by weight
5	(1) Tallow	20.0
	(2) Coconut oil	12.0
	(3) Castor oil	5.0
	(4) Olive oil	3.0
10	(5) Caustic potash	6.0
	(6) Ethanol	20.0
	(7) Glycerine	5.0
15	(8) Sucrose	10.0
	(9) Cyclohexylguanidine	3.0
	(10) EDTA	0.1
20	(11) Perfume	q.s.
	(12) Dye	q.s.
	(13) Purified water	balance

Example II-9 Liquid soap

25	(1) Lauric acid	3.0
	(2) Myristic acid	7.0
	(3) Palmitic acid	3.0
30	(4) Oleic acid	2.5
	(5) Lauroyl diethanolamide	6.0
	(6) Propylene glycol	11.0
35	(7) Glycerine	4.0
	(8) Sucrose	5.0
	(9) Caustic potash	3.0
	(10) EDTA	0.1
40	(11) p-Nitrophenyl-p'-guanidinobenzoic acid	0.1
	(12) Perfume	q.s.
	(13) Purified water	balance

45 The respective compounds used in the following Examples were the compounds represented by the formula shown below, in which R_1 , R_2 , R_3 are respectively those shown in Table II-4.

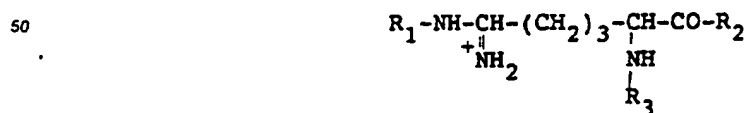
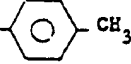
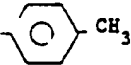
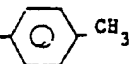
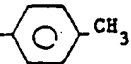


Table II-8

	R ₁	R ₂	R ₃
Compound II-1	D-Phe-Pro	CH ₂ Cl	SO ₂ - 
Compound II-2	Glu-Gly	CH ₂ Cl	SO ₂ - 
Compound II-3	Ile-Glu-Gly	CH ₂ Cl	SO ₂ - 
Compound II-4	Pro-Phe	CH ₂ Cl	SO ₂ - 

(Phe: phenylalanine, Pro: proline, Glu: glutamic acid, Gly: glycine, Ile: isoleucine)

Example II-10 Cleansing cream

	% by weight
(1) Solid paraffin	3.5
(2) Microcrystalline wax	8.0
(3) Beeswax	5.0
(4) Petroplatum	1.0
(5) Fluid paraffin	43.0
(6) Glycerin monooleate	4.0
(7) POE (20 mole) monooleate	0.5
(8) Compounds II-1	5.0
(9) Perfume	q.s.
(10) Purified water	balance

Example II-11 Emulsified type cleansing lotion

	% by weight
(1) Stearic acid	3.0
(2) Cetyl alcohol	1.0
(3) Petrolatum	4.5

	(4)	Fluid paraffin	11.0
	(5)	POE (20 mole) oleyl alcohol ether	1.5
5	(6)	POE (5 mole) sorbitane monolauric acid ether	1.0
	(7)	Triethanolamine	1.0
10	(8)	Propylene glycol	6.0
	(9)	Compound II-2	1.0
	(10)	Perfume	q.s.
	(11)	Purified water	balance

15 Example II-12 Non-emulsified type cleansing lotion
% by weight

	(1)	Propylene glycol	10.0
20	(2)	Dipropylene glycol	6.0
	(3)	N,N-dimethyl-lauryl-N-carboxymethyl-ammoniumbetaine	2.0
25	(4)	POE (20 mole) sorbitane monolauric acid ether	3.0
	(5)	Ethyl alcohol	10.0
	(6)	Compound II-3	5.0
30	(7)	Perfume	q.s.
	(8)	Purified water	balance

35 Example II-13 Aerosol shaving foam

	(Filling recipe)	% by weight
	(1) Stearic acid	5.5
	(2) Purified coconut fatty acids	1.5
40	(3) Glyceryl monostearate	5.0
	(4) Glycerine	10.0
	(5) Triethanolamine	4.0
	(6) Compound II-4	0.05
45	(7) Perfume	q.s.
	(8) Purified water	balance

(Filling recipe)

50	(1)	Stock solution	94.0
	(2)	LPG	6.0

Examples II-8 to II-13 were found to perfectly harmless and to have a strong washing power.

55 **Claims**

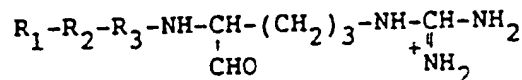
1. A washing composition comprising at least one compound having a protease inhibitory activity and

dermatologically acceptable components for a conventional washing composition.

2. A washing composition as claimed in claim 1, wherein said compound is contained in an amount of 0.0001% to 20% by weight based on the total amount of the composition.

3. A washing composition as claimed in claim 1 or 2 wherein said compound is at least one compound derived from animals or vegetables selected from the group consisting of a bovine pancrea basic trypsin inhibitor, aprotinin, soybean trypsin inhibitor, lima bean protease inhibitor, and corn protease inhibitor.

4. A washing composition as claimed in claim 1 or 2 wherein said compound is at least a derived from microorganisms component selected from the group consisting of antipine, plasminostreptin and compounds comprehensively known as leupeptine represented by the following formula :



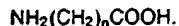
- 20
- $R_1 = \text{CH}_3\text{CO}, \text{CH}_3\text{CH}_2\text{CO}$
 $R_2 = \text{L-Leu}, \text{L-Ile}, \text{L-Val}$
 $R_3 = \text{L-Leu}, \text{L-Ile}, \text{L-Val}$
 (Leu: leucine, Ile: isoleucine, Val: valine)

- 25 5. A washing composition as claimed in claim 1 or 2 wherein said compound is at least one compound selected from the group consisting of benzamidine, p-aminobenzamidine, m-aminobenzamidine, phenylguanidine, (2R,4R)-4-methyl-1-[N²-(3-methyl-1,2,3,4-tetrahydro-8-quinolinesulfonyl)-L-arginy]-2-piperidinecarboxylic acid monohydrate, and dancylarginine N-(3-ethyl-1,5-pentanediy)amide.

- 30 6. A washing composition as claimed in claim 1 or 2 wherein said compound is at least one compound selected from the group consisting of acetamide and the derivatives thereof.

7. A washing composition as claimed in claim 1 or 2 wherein said compound is at least one compound selected from the group consisting of guanidine and the derivatives thereof.

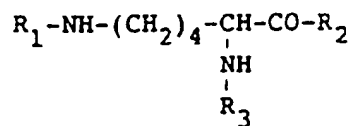
8. A washing composition as claimed in claim 1 or 2 wherein said compound is at least one ω -amino acid selected from the group consisting of tranexamic acid, p-aminomethylbenzoic acid, 4-aminomethylbicyclo(2.2.2)octane-1-carboxylic acid, 5-[trans-4(aminomethyl)-cyclohexyl]tetrazole, 3-[trans-4(aminomethyl)cyclohexyl]-2-oxopropionate, trans-4(aminomethyl)cyclohexyl glyoxal monohydrate, and trans-4(aminomethyl)cyclohexane hydroxamic acid, or substances represented by the following formula wherein the carbon chain has $n = 1 - 8$):



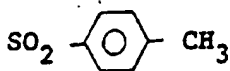
9. A washing composition as claimed in claim 1 or 2 wherein said compound is at least one component selected from the group consisting of fluorophosphoric acid, fluoro sulfonic acid, and the derivatives thereof.

10. A washing composition as claimed in claim 1 or 2 wherein said compound is at least one component selected from the group consisting of p-nitrophenyl-p'guanidinobenzoic acid, 3',6'-bis(4-guanidinobenzoyloxy)-5-(N'-(4-carboxyphenyl)thioureidospiro[isobenzofuran-1(3H) 9'-(9H)xanthen]-3-one.

- 55 11. A washing composition as claimed in claim 1 or 2 wherein said compound is at least one component selected from the group consisting of compounds represented by the following formula:

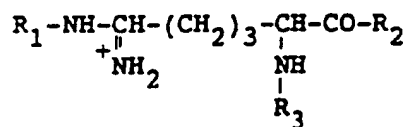


R_1 = H, Phe-Ala, Ala-Phe
 R_2 = OH, CH_2Cl
 R_3 = H,

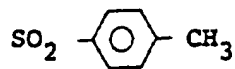


(Phe: phenylalanine, Ala: alanine)

12. A washing composition as claimed in claim 1 or 2 wherein said compound is at least one component selected from the group consisting of the compounds represented by the following formula:



R_1 = H, D-Phe-Pro, Glu-Gly, Ile-Glu-Gly, Pro-Phe, Ala-Phe
 R_2 = OH, CH_2Cl
 R_3 = H,



(Phe: phenylalanine, Pro: proline, Glu: glutamic acid, Gly: glycine, Ile: isoleucine, Ala: alanine)



European
Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 40 2307

DOCUMENTS CONSIDERED TO BE RELEVANT					
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)		
X	FR-A-2 216 986 (BAYER AG) * page 2, line 3 - line 15 ** - - -	1-3	A 61 K 7/48 C 11 D 3/33		
A	FR-A-2 216 986 (* page 5, line 1 - line 6; claims 1,2; example 4) - - -	4			
X	DE-A-1 939 419 (BAYER AG) * the whole document ** - - -	1-3			
X	FR-A-2 016 080 (HOECHST AG) - - -	1,2,8			
A	FR-A-2 016 080 () * claims; examples ** - - -	11			
X	DE-A-1 944 568 (HENKEL) * page 4, line 6 - line 18; claim 1; examples 3,4 ** - - -	1,2,6			
X	US-A-4 566 985 (L.C. BRUNO ET AL.) * claim 1; examples ** - - -	1,2,5			
X	DE-A-2 401 752 (UNILEVER) * claims 1,2 ** - - -	1,2,8	TECHNICAL FIELDS SEARCHED (Int. Cl.5)		
X	WORLD PATENTS INDEX LATEST Derwent Publications Ltd., London, GB; AN 85-226613 (37) & JP-A-60 146 815 (LION CORP.) 2 August 1985 * abstract ** - - -	1,2,8	C 11 D A 61 K		
X	WORLD PATENTS INDEX LATEST Derwent Publications Ltd., London, GB; AN 81-03134D (03) & JP-A-55 145 798 (SANYO CHEM.) 14 November 1980 * abstract ** - - -	1,2,9			
		-/-			
The present search report has been drawn up for all claims					
Place of search The Hague		Date of completion of search 28 November 91	Examiner GRITTERN A.G.		
<table border="0"><tr><td>CATEGORY OF CITED DOCUMENTS X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention</td><td>E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons ----- &: member of the same patent family, corresponding document</td></tr></table>				CATEGORY OF CITED DOCUMENTS X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention	E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons ----- &: member of the same patent family, corresponding document
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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CLS)
A	FR-A-2 457 891 (AJINOMOTO) "examples 30,33" .. -----	1,11,12	
			TECHNICAL FIELDS SEARCHED (Int. CLS)
The present search report has been drawn up for all claims			
Place of search		Date of completion of search	Examiner
The Hague		28 November 91	GRITTERN A.G.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention</p> <p>E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons S: member of the same patent family, corresponding document</p>			